## REMARKS

### AMENDMENTS TO THE SPECIFICATION

The Title of the specification was amended to substitute the phrase "Identification And Modulation Of A" with the phrase "METHODS OF DIAGNOSING TUMORS USING THE", as well as to delete the phrase ", ASSOCIATED WITH CHRONIC OBSTRUCTIVE PULMONARY DISEASE (COPD) AND NF-κB AND E-SELECTIN REGULATION". These amendments were made solely to make the Title consonant with the claimed invention. Support for these amendments may be found on pages 10 to 13, in Figures 16 to 18, and throughout the specification as originally filed. No new matter has been added.

## STATUS OF THE CLAIMS

Claims 1 to 34 were cancelled.

Claims 35 and 36 were amended.

Claims 37 and 39 to 44 are withdrawn.

Claims 35, 36, and 38 are pending.

Claim 35 has been amended to substitute the term "polypeptide" within the phrase "said polypeptide" as found within sub clause "b)" to ensure proper antecedent basis is maintained. Claim 35 was further amended to substitute the term "comprising" with the phrase "consisting of". Support for this amendment may be found on page 84 (e.g., "RAI-3 polypeptide comprising, or alternatively, consisting of, ... the polypeptide having an amino acid sequence of SEQ ID NO:1 or SEQ ID NO:3"). Applicants assert that these amendments were not made to overcome any issues related to the patentability of this claim and that Applicants right to equivalents of Claim 35 is reserved. No new matter has been added.

Claim 36 has been amended to delete sub clauses (j) thru (q), and to "renumber" sub clauses (r) to (u) with the following sub clauses (j) to (m) to take into account the deletion of original sub clauses (j) thru (q). Claim 36 was further amended to substitute the term "comprising" with the phrase "consisting of" in each of sub clauses (a) thru (i) and in new sub clauses (j) thru (m). Applicants assert that this amendment was not made to overcome any issues related to the patentability of this claim and that Applicants right to equivalents of Claim 36 is reserved. No new matter has been added.

## I. Rejections under 35 U.S.C. § 112, First Paragraph

**a.** The Examiner has rejected Claim 35, 36, and 38 under 35 U.S.C. § 112, first paragraph, alleging that these claims contain subject matter which was not described in the specification in such a way as to enable one skilled in the art to make and use the invention.. More particularly, the Examiner alleges:

> Claims 35, 36, and 38 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of diagnosing breast cancer in a sample by determining the expression level of RNA encoding the polypeptide of SEQ ID NO: 3 comprising specific hybridizing between said RNA to the complementary sequence of SEQ ID NO: 2 or its coding sequence, does not reasonably provide enablement for the instantly claimed method comprising hybridizing between said RNA to the complementary sequence of a nucleic acid *comprising* a fragment of SEQ ID NO: 2, a nucleotide sequence encoding the amino acid sequence of SEQ ID NO: 3 or a fragment thereof. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.
>
> . . .
>
> The claims are broad and are drawn to a method of diagnosing breast cancer using a genus of nucleic acids. While providing sufficient guidance and/or working examples on how to determine the expression level of mRNA encoding the polypeptide of SEQ ID NO: 3 in various normal tissues (Fig. 5) and tumor tissues (breast, stomach tumors, and testicular tumors) (see, e.g., Example 11, Fig. 16-18), using quantitative PCR analysis and specific primers and probe (page 213), the specification fails to provide sufficient guidance/direction or working examples on how to diagnose breast cancer by hybridizing mRNA in a breast tumor sample with a genus of nucleic acids, including a complementary sequence of a nucleic acid *comprising* a fragment of SEQ ID NO: 2, a nucleotide sequence encoding the amino acid sequence of SEQ ID NO: 3 or a fragment thereof. Thus, use of a complementary sequence of these nucleic acids in the measurement of mRNA level by hybridization may measure an mRNA that is distinct from the present mRNA. The state of the art is such that determining the specificity of hybridization is empirical by nature and the effect of mismatches is unpredictable, as taught by Wallace et al. (Methods Enzymol. 152:432-443, 1987) and Sambrook et al. (Molecular Cloning, A Laboratory Manual, 2nd Edition, 1989, Cold Spring Harbor Laboratory, Cold Spring Harbor, NY, page 11.47).
>
> The prior art (see, e.g., U.S. Patent No. 6812339; U.S. Patent Application Publication No. 20030113798A1) teaches an isolated nucleic acid molecule that is 100% identical to SEQ ID NO: 2 and encodes a polypeptide that is 100% identical to SEQ ID NO: 3 of the present invention (see attached sequence alignment). Veiby et al. (U.S. Pub. No. US2003/0068636 A1, April 10, 2003; 102(e) date: 06/21/2001) teach a diagnostic method of assessing whether a patient is afflicted with breast cancer comprising determining the expression level of RNA encoding the polypeptide of SEQ ID NO: 2 (see sequence alignment). However, none of the prior art teaches diagnosing breast cancer by

hybridizing mRNA in a breast tumor sample with a complementary sequence of a nucleic acid *comprising* a fragment of SEQ ID NO: 2, a nucleotide sequence encoding the amino acid sequence of SEQ ID NO: 3 or a fragment thereof.

While an artisan has a high level of skill in determining expression profile of an mRNA in normal tissues and tumor samples and diagnosing tumors, such as breast cancer, the recited use of a genus of nucleic acids in the .claimed methods would require an artisan to carry out undue experimentation to practice the claimed invention.

Accordingly, in view of the factors discussed above, it would require undue experimentation for one skilled in the art to use the invention commensurate in scope with these claims.

Applicants disagree with the Examiners allegation that Claims 35, 36, and 38 are not enabled for diagnosing breast cancer by "hybridizing mRNA in a breast tumor sample with a genus of nucleic acids". Specifically, Applicants point out that each of the sequences listed in Claim 36 (a) to (i) and (r) to (u) is directly derived from the coding region of SEQ ID NO:3 thus would be expected to hybridize to the coding region of SEQ ID NO:3. In addition, Applicants point out that none of the sequences encompassed by these sub clauses represent a genus , on one hand, nor is the claim itself directed to a genus on the other hand since Claim 36 is a Markush-type claim. Regarding, the Claim 36 sub clauses (j) to (q), while these sequences do encompass a genus (i.e., more than one sequence is encompassed by each amino acid range due to the degeneracy of the genetic code), a skilled artisan would appreciate that such a degenerate sequence would be expected to hybridize to the coding region of SEQ ID NO:3. However, in the sole interest of facilitating prosecution, Applicants have amended Claim 36 to delete sub clauses (j) to (q).

In addition, Applicants also disagree with the Examiner's allegation that Claims 35, 36, and 38 are not enabled for the use of "a complementary sequence of a nucleic acid comprising a fragment of SEQ ID NO:2" and "a nucleotide sequence encoding the amino acid sequence of SEQ ID NO:3 or a fragment thereof" with particular emphasis on the use of the "comprising" term. In particular, Applicants argue a skilled artisan would appreciate that if a specific fragment of a target sequence hybridizes to a target sequence, then a longer fragment of the target sequence would also be expected to hybridize to the same target sequence. Since the sequences encompassed by Claim 36 (a) to (i) and (r) to (u) are directly derived from the coding region of SEQ ID NO:3, they would clearly be expected to hybridize to SEQ ID NO:3 and thus longer versions of these sequences would also be expected to hybridize. However, in the sole interest of facilitating prosecution, Applicants have amended Claims 35 and 36 to substitute the term "comprising" with the phrase "consisting of"

in each instance in sub clause (a) and in sub clauses (a) thru (u), respectively. Applicants believe the Examiners rejection of Claims 35 and 36 has been overcome in consideration of Applicants amendments and respectfully request withdrawal of the Examiner's rejection under 35 U.S.C. § 112, first paragraph. Since Claim 38 depends from Claims 35 or 36, Applicants believe the Examiners rejection of Claim 38 has also been overcome, in consideration of Applicants amendments and respectfully request withdrawal of the Examiner's rejection under 35 U.S.C. § 112, first paragraph.

Re: Claim 35, Applicants disagree with the Examiner's allegation. However, in the sole interest of facilitating prosecution, Applicants have amended Claim 35 to substitute the term "comprising" with the phrase "consisting of". Accordingly, Applicants believe the Examiner's rejection of Claim 35 under 35 U.S.C. § 112, first paragraph has been overcome in consideration of this amedment. Since Claim 38 depends from Claim 35, Applicants believe the Examiners rejection of Claim 38 under 35 U.S.C. § 112, first paragraph, in part, should also be withdrawn.

## II. Rejections under 35 U.S.C. § 112 – Second Paragraph

**a.** The Examiner has rejected Claims 35, 36, and 38 under 35 U.S.C. § 112, second paragraph, as being "indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention." More particularly, the Examiner states:

> Claim 35 is indefinite because it, in part b), recites "said expression level of said polypeptide". It is clear from part a) of the claim that the expression level of RNA, not the expression level of polypeptide, is determined.
>
> Claims 36 and 38 are rejected as dependent claims from claim 35.

In response, Applicants have amended Claim 35 to substitute the phrase "said polypeptide" with the phrase "said RNA" in each instance. Applicants believe the Examiner's rejection of Claim 35 under 35 U.S.C. § 112, second paragraph, has been overcome in consideration of this amendment. Since Claims 36 to 38 depend from Claim 35, directly or indirectly, Applicants believe the Examiner's rejection of these claims under 35 U.S.C. § 112, second paragraph, has also been overcome in consideration of this amendment.

## IV. Rejections under 35 U.S.C. § 102(e)

**a.** The Examiner has rejected Claims 35, 36, and 38 under 35 U.S.C. § 102(e) as being anticipated by Veiby et al. (U.S. Pub. No. US2003/0068636 A1, April 10, 2003; 102(e) date: 06/21/2001). More particularly, the Examiner alleges

> Veiby et al. teach a nucleic acid marker (SEQ ID NO: 59) for breast cancer (see Table 2) that comprises the coding sequence of SEQ ID NO: 2 of the present invention and encodes a protein (SEQ ID NO: 60) that is 100% identical to the polypeptide of SEQ ID NO: 3 of the present invention (see attached sequence alignment). Veiby et al. teach a diagnostic method of assessing whether a patient is afflicted with breast cancer comprising determining the level of expression of a marker of the invention in a patient sample and the normal level of expression of the marker in a control non-cancerous breast sample. A significantly higher level of expression of the nucleic acid marker in the patient sample as compared to the normal level is an indication that the patient is afflicted with breast cancer ([0020] to [0023]). Veiby et al. further teach that expression of a nucleic acid marker can be assessed by preparing mRNA/cDNA from cells in a patient sample, and by hybridizing the mRNA/cDNA with a reference polynucleotide which is a complement of a marker nucleic acid, or a fragment thereof ([0122]). Thus, the teachings of Veiby et al. meet the limitations of claims 35, 36, and 38.

Applicants disagree with the Examiner's allegation. However, in the sole interest of facilitating prosecution, Applicants have amended Claim 35 to substitute the term "comprising" with the phrase "consisting of". Applicants believe the Examiner's rejection of Claim 35 under 35 U.S.C. § 102(e) has been overcome in consideration of this amendment since Veiby et al. fails to teach all of the elements of Claim 35 on account of it not disclosing a "polypeptide consisting of the sequence of amino acids 2 to 357 of SEQ ID NO:3". Accordingly, Applicants believe the Examiner's rejection of Claim 35 under 35 U.S.C. § 102(e) has also been overcome in consideration of this amendment. Since Claim 36 and 38 depend from Claim 35, Applicants believe the Examiner's rejection of Claims 36 and 38 under 35 U.S.C. § 102(e) has also been overcome in consideration of this amendment.

Applicants believe that all of the Examiners rejections and objections have been overcome and that all of the pending claims before the Examiner are in condition for allowance. An early Office Action to that effect is, therefore, earnestly solicited.

A three-month extension is hereby requested pursuant to 37 CFR §1.136(a). Please charge Deposit Account No. 19-3880 in the name of Bristol-Myers Squibb Company in the amount of $1020 for payment of the extension fee.

If any fee is due in connection herewith not already accounted for, please charge such fee to Deposit Account No. 19-3880 of the undersigned. Furthermore, if any extension of time not already

accounted for is required, such extension is hereby petitioned for, and it is requested that any fee due for said extension be charged to the above-stated Deposit Account.

Respectfully submitted,

Stephen C. D'Amico
Agent for Applicants
Reg. No. 46,652

Bristol-Myers Squibb Company
Patent Department
P.O. Box 4000
Princeton, NJ 08543-4000
(609) 252-5289

Date: January 30, 2007